REMARKS

Status of the Claims

Claims 1-7 are pending. Claims 1-5 are withdrawn from consideration. Claims 1-5 and 7 are canceled herein. Claims 6-7 are rejected. No new matter is added.

Amendments to the claims

Claim 6 is amended to overcome the 35 U.S.C. §103(~~b~~a) rejection as discussed *infra*. The limitation of claim 7 is incorporated into claim 6 and P-selectin deleted from the claim. Additionally, the claim is amended to clarify that the endothelial cell is on the irradiated tissue or organ. Claim 7 is canceled. No new matter has been added.

The 35 U.S.C. §103(a) rejection

The rejection of claims 6 and 7 under 35 U.S.C. §103(a) is maintained, as being unpatentable over **Hallahan** *et al.* (U.S. 6,159,443), in view of the fact disclosed in the specification on pages 4, lines 15-20; 5, lines 1-5; and 10, lines 12-20, and

Mastrobattista *et al.*, (*Biochim. Biophys. Acta*, 1999, 1419: 353-363). This rejection is respectfully traversed.

The Examiner states that **Hallahan** *et al.* teach a method of treating cancer by exposing target tissue/organ to ionizing radiation and administering biodegradable particles bearing antibody or antibody fragments specific for P-selectin (col. 8, ll 17-21) that bind to a cellular adhesion molecule expressed on endothelial cells (col. 7-8). Additionally, the specification teaches that exposure of diseased tissue to irradiation causes an increase in expression of P-selectin and ICAM-1 on endothelial cells (pg. 4, ll. 15 to pg. 5, ll. 5; pg. 10, ll. 12-20). Furthermore, **Mastrobattista** *et al.* teach that biomolecular carriers bearing anti-ICAM-1 antibodies can be effectively used to deliver drugs to sites where expression of ICAM-1 is increased (entire disclosure particularly Abstract).

The Examiner states that it would have been obvious to one skilled in the art to apply the teachings of **Mastrobattista** *et al.* and the specification of **Hallahan** *et al.*, and substitute biomolecular carrier bearing antibodies to one cellular adhesion molecule (P-selectin) to biomolecular carrier bearing antibodies to another cellular adhesion molecule (ICAM-1), because the expression of either one of them would be enhanced in target tissue

after irradiation, to obtain the claimed method of treating cancer by irradiating a target tissue or organ and administering the biomolecular carrier bearing antibodies specific to ICAM-1. Applicants respectfully disagree.

In a prima facie case of obviousness, the combination of the references must teach all the elements of the invention. Additionally, one must consider what is fairly taught in the references. **Hallahan** *et al.* teach an active agent delivered by an x-ray guided delivery vehicle to treat a neoplasm that preferably is a platelet or a leukocyte or more preferably is a protein/peptide, an antibody, a microsphere coated with a protein/peptide or a liposome conjugated to platelets, leukocytes, or proteins/peptides all of which bind to activated platelets (Abstract; col. 7, ll. 37 to col. 8, ll. 10). Additionally, **Hallahan** *et al.* teach an antibody, i.e., anti-P-selectin and anti-E-selectin, conjugated to I-131 and targeted to the vascular endothelium of tumors (see col. 39, ll. 65 to col. 40, ll. 12).

Mastrobattista *et al.* specifically teach that ICAM-1 targeted immunoliposomes bind to bronchial epithelial cells *in vitro* in a concentration dependent manner and may be used as carriers for the intracellular delivery of anti-inflammatory drugs to sites of

inflammation characterized by an increased expression of ICAM-1 (Abstract). The instant specification teaches that irradiating diseased tissue causes an increase expression of P-selectin and ICAM-1.

As amended, Applicants' invention is drawn to a method of treating cancer by irradiating the cancerous tissue/organ and administering a biodegradable particle comprising an antibody/Ab fragment that binds to ICAM-1 on endothelial cells and a pharmaceutical. The specification defines a biodegradable particle as comprising biodegradable polymers or PEGylated copolymers, as are known in the art, formed as a microsphere or nanosphere (pg. 24, ll. 11 to pg. 25, ll. 15). Considering these amendments in view of the teachings in the prior art, Applicants submit that it would not be obvious to substitute ICAM-1 as taught by **Mastrobattista** *et al.* for P-selectin as taught by **Hallahan** *et al.*

The Examiner stated that **Hallahan** *et al.* provide motivation in teaching that there is a substantial need for an improved method for a selective delivery of therapeutic or imaging agents using a biomolecular carrier bearing antibodies to cellular adhesion molecule that overexpressed on endothelial cells (Paper No. 9, pg. 4). Respectfully, this is a general motivation for any

practioner of this particular art including Applicants. **Hallahan** *et al.* were motivated by the unexpected observation that P-selectin is localized in the vascular lumen of tumor blood vessels and that platelets express P-selectin and aggregate in tumor vessels when the tumor is irradiated (col. 3, ll. 20-31). As such, **Hallahan** *et al.* designed a delivery vehicle to target activated platelets.

No suggestion is found in **Hallahan** *et al.* that a delivery vehicle comprising an antibody specific for other than platelet antigens, such as anti-P-selectin, anti-GP-IIb or anti-GP-IIIa, would provide a selective targeting method having a reasonable expectation of success. Indeed, in the one example where radiolabeled anti-P-selectin and anti-E-selectin were targeted to vascular endothelium after radiation, E-selectin demonstrated non-specific targeting to normal tissue (col. 40, ll. 20-23).

Although **Mastrobattista** *et al.* teach specificity of an anti-ICAM liposome to bronchial epithelial cells, they only theorize that such conjugates could be used in targeted delivery of anti-inflammatory agents to ICAM-1 expressing cells at sites of inflammation. This is not a clear nor a reasonable suggestion that anti-ICAM-1 immunoliposomes would successfully target ICAM-1 expressing cells to effectively deliver an agent, but merely a

statement of intent to investigate the possibility with no suggestion of that such attempts would be successful.

Even given that the specification teaches irradiation of diseased tissue upregulates ICAM-1 expression, at best one of ordinary skill in the art could only try to substitute delivery vehicles binding to ICAM-1 on irradiated endothelial cells for the delivery vehicles in **Hallahan** *et al.* Obvious to try has long been held not to be the standard for obviousness. At best one of ordinary skill in the art would find that **Mastrobattista** *et al.* only suggest that one of ordinary skill in the art try an *in vivo* targeted immunoliposomal system specific for ICAM-1 and would find no suggestion in **Hallahan** *et al.* that anti-ICAM-1 delivery vehicles would selectively target irradiated neoplasms. In fact, **Hallahan** *et al.* teach that a different selectin, E-selectin, does not demonstrate specificity to neoplastic tissue. Any suggestion that a delivery vehicle, i.e., the biodegradable particles in the instant invention, linked to an antibody specific for ICAM-1 would selectively target irradiated endothelial cells in cancerous tissues/organs must come from the instant application.

Thus, Applicants submit that, as a teaching or suggestion to make the claimed combination and the reasonable expectation of

success must both be found in the prior art, not in Applicants' disclosure, a *prima facie* case of obviousness has not been established. Accordingly, in view of the arguments presented *supra*, Applicants' respectfully request that the rejection of claims 6-7 under 35 U.S.C. 103(a) is withdrawn.

This is intended to supplement the response filed, June 9, 2003, to the Final Office Action mailed April 8, 2003. Applicants enclose herewith a Petition for Extension of Time under 37 C.F.R. 1.136. Please debit the $205 extension fee under 37 C.F.R. 1.17(a)(2) or any additional applicable fees from Deposit Account No. 07-1185. If any issues remain outstanding, the Examiner is respectfully requested to telephone the attorney of record identified *supra* for immediate resolution.